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Cancer mortality in long-term survivors of retinoblastoma

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ABSTRACT

This study examined long-term cause-specific mortality among 998 Dutch retinoblastoma survivors, diagnosed from 1862 to 2005, according to follow-up time, treatment and heredity. After a median follow-up of 30.8 years, only cause-specific mortality for second malignancies among hereditary retinoblastoma survivors was statistically significantly increased with 12.8-fold. Risk of death from second malignancies among non-hereditary survivors was not increased. Mortality rates of second malignancy among hereditary patients were non-significantly elevated with 1.6-fold for treated with radiotherapy, compared to those treated otherwise. Standardised mortality ratios (SMRs) for second malignancy among hereditary patients increased during the first three decades after retinoblastoma diagnosis. Whereas these risks decreased after three decades, the absolute excess risk (AER) increased significantly, up to 23.2 excess cases per 1000 patients/year after five decades of follow-up. Fifty years after retinoblastoma diagnosis the cumulative mortality from any second malignancy was 17.3% for hereditary patients. Very long-term follow-up of retinoblastoma patients revealed an emerging excess risk of mortality in hereditary retinoblastoma survivors. This implies that lifelong follow-up is needed, whereas at the same time, patients and their physicians must be alerted to the increased second malignancy risks.

1. Introduction

Retinoblastoma is a rare childhood cancer of the eye. The disease is caused by a *RB1* gene mutation in all patients with bilateral retinoblastoma, as well as in 10% of those with unilateral retinoblastoma.[1] Nowadays children diagnosed with retinoblastoma in the western world have excellent cure rates (up to 99%).[2] However, hereditary retinoblastoma survivors are at an exceptionally high risk of developing subsequent primary malignancies in childhood and adolescence.[3–13] So far, little information is available on long-term excess mortality among survivors of retinoblastoma.[7,14,15] Published studies include few patients with more than 50 years of follow-up, implying that mortality risk of retinoblastoma survivors has been hardly examined at ages during which death rates increase in the general population.

The national retinoblastoma registry of the Netherlands includes 1068 retinoblastoma patients diagnosed since 1862. Therefore, the registry offers a unique opportunity to analyse cause-specific mortality after long-term follow-up in a large group of retinoblastoma survivors, according to treatment and heredity.

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2. Materials and methods

2.1. Study population

The cohort analysed in this study has been described previously.[13] In brief, the cohort includes 1068 Dutch retinoblastoma patients diagnosed from 1862 to 2005. For each patient data were collected concerning demography, family history of retinoblastoma, tumour laterality, treatment for retinoblastoma (including radiotherapy fields and energy type, and chemotherapeutic agents), second and subsequent cancers and date and (underlying) cause of death. If a cohort member had died, the date, the place of death and the death certificate number were recorded. Information on the cause of death was obtained from Statistics Netherlands for all deceased cohort members up to June 2007. All causes of death in The Netherlands are coded by trained nosologists at Statistics Netherlands who use the International Classification of Diseases,[16] applicable to the particular calendar period. For this study, all registered causes of death coded on the basis of earlier revisions were reclassified according to the 10th revision.

Mortality rates in The Netherlands have been available since 1875, although only few causes of death were distinguished at that time. Throughout the decades, more and more causes of death were added to the ICD-classification and detailed cause-specific mortality rates were available since 1961. However, for skin melanoma and breast cancer reference rates were available since 1901.[17]

From the 1068 Dutch retinoblastoma patients, we excluded six patients because they apparently had retinomas (tumours with spontaneous growth arrest), 29 patients who died before 1901, and four patients with an unknown birth date, which left 1029 (96%) retinoblastoma patients eligible for this study. After extensive follow-up procedures,[13] we had to exclude 31 (3%) patients who were lost to follow-up.

Patients with bilateral disease, a positive family history of retinoblastoma or a defect in the *RB1* gene found in chromosomal/DNA analysis were classified as hereditary (39.6%). Patients with unilateral retinoblastoma, no family history of retinoblastoma or no defect found in the *RB1* gene were classified as non-hereditary (60.4%).

This study was approved by the Medical Ethics Committees of all participating hospitals, and was conducted in accordance with the principles of the Helsinki declaration.

2.2. Statistical analysis

A comparison was made between cause-specific mortality in retinoblastoma survivors and the Dutch population. In this person-years type of analysis, the ratio of the observed (O) to the expected (E) number of deaths in the study population was determined using age-, sex- and calendar period-specific mortality rates from Statistics Netherlands. To estimate standardised mortality ratios (SMRs) of breast cancer and skin melanoma, follow-up for mortality began on 1st January 1901, when reference rates for breast cancer and melanoma became available. For all other causes of death the comparison with mortality rates in the general population was restricted to those patients who were still alive in 1960, or born after 1960 ($n = 849$). Consequently, in analyses on causes of death other than breast cancer and skin melanoma, time at risk began on 1st January 1961. Follow-up ended at the date of death, date of emigration or the closing date of our study, whichever occurred first.

The SMR was calculated as the ratio of the observed to the expected number of deaths, and a 95% confidence interval (CI) was calculated based on the Poisson distribution.[18] Absolute excess risk (AER) is the most appropriate risk measure to judge which specific causes contribute most to excess mortality. The AER was calculated by subtracting the expected number of cases from the number observed, divided by person-years at risk multiplied by 1000. Multivariable Cox regression analysis was performed to quantify the effects of heredity and treatment on mortality, adjusting for confounders. Cox models were fitted using SPSS statistical software (SPSS, Chicago, IL). Cumulative risks of death by type of retinoblastoma and treatment were calculated with adjustment for competing risks of death due to other causes using S-plus statistical software (Insightful, Seattle, WA), including user-written functions.[19]

3. Results

Table 1 shows the general characteristics of the study population; retinoblastoma patients diagnosed between 1862 and 2005, who were at risk of death between January 1901 and June 2007. The median follow-up time for hereditary retinoblastoma survivors was 25.8 years (range = 0.13–79.9 years). For non-hereditary retinoblastoma survivors, the median follow-up was 34.2 years (range = 0.01–89.7 years). Most of the hereditary patients (56.2%) were treated with radiotherapy for their retinoblastoma, whereas only 6.3% of the non-hereditary patients were treated with radiotherapy. Most of the non-hereditary patients (88.2%) were treated with surgery alone. Chemotherapy was used with or without combination of radiotherapy for about 18.8% of the hereditary patients and in 2.8% of the non-hereditary patients. Of the 849 retinoblastoma patients with follow-up from January 1961, 60 (7.1%) were diagnosed with retinoblastoma from 1891 to 1929, 417 (49.1%) from 1930 to 1969 and 372 (43.8%) from 1970 to 2005. Percentages of hereditary and non-hereditary patients were similar to those for all patients (39.7% versus 60.3%, respectively). The median follow-up time for retinoblastoma patients at risk of death after 1960 was 30.8 years (range = 0.13–79.9 years) for hereditary retinoblastoma patients and 39.1 years (range = 0.01–89.7 years) for non-hereditary retinoblastoma patients.

Table 2 shows observed numbers of cause-specific deaths among hereditary and non-hereditary retinoblastoma patients, and provides separate data with SMRs for those who died after January 1, 1961. A total of 332 deaths were observed, for which 316 death certificates were obtained (95%). By far the most important cause of death was retinoblastoma ($n = 156$, 47.0%). Of these retinoblastoma deaths, more than 70% occurred before 1961. Seven patients suffered from fatal pinealoblastoma. For these patients the cause of death was recorded as retinoblastoma. Fig. 1 shows that retinoblastoma death impressively decreased over time.

Among the 849 retinoblastoma survivors at risk of death after January 1, 1961, a total of 182 deaths were observed.

Table 1 – Characteristics of Dutch retinoblastoma patients diagnosed between 1862 and 2005 and at risk of death between January 1901 and June 2007.[a]

Characteristics	Hereditary No. of patients (%)	Non-hereditary No. of patients (%)	Total No. of patients (%)
Total no. of patients	395 (100)	603 (100)	998 (100)
Sex			
Male	201 (50.9)	328 (54.4)	529 (53)
Female	194 (49.1)	275 (45.6)	469 (47)
Age at retinoblastoma diagnosis			
<1	298 (75.5)	204 (33.8)	502 (50.3)
1–2	57 (14.4)	122 (20.2)	179 (17.9)
2+	40 (10.1)	277 (46.0)	317 (31.8)
No. of subjects entering each follow-up interval, years			
0–9	395 (100)	603 (100)	998 (100)
10–19	272 (68.9)	453 (75.1)	725 (72.6)
20–29	225 (60.0)	386 (64.0)	611 (61.2)
30–39	179 (45.3)	323 (53.6)	502 (50.3)
40–49	121 (30.6)	254 (42.1)	375 (37.6)
50–59	73 (18.5)	158 (26.2)	231 (23.1)
60+	27 (6.8)	82 (13.6)	109 (10.9)
Treatment for retinoblastoma			
Surgery only	136 (34.4)	531 (88.1)	667 (66.8)
Chemotherapy only	16 (4.1)	9 (1.5)	25 (2.5)
Radiation only	164 (41.5)	30 (5.0)	194 (19.4)
Radiation, chemotherapy	58 (14.7)	8 (1.3)	66 (6.6)
Laser coagulation only	4 (1.0)	1 (0.2)	5 (0.5)
Missing	17 (4.3)	24 (4.0)	41 (4.1)
Vital status at the end of follow-up			
Alive	238 (60.3)	428 (71.0)	666 (66.7)
Dead	157 (39.7)	175 (29.0)	332 (33.3)

a Percentages for some categories do not total 100 because of rounding.

There were 40 deaths due to retinoblastoma, and 142 deaths due to other causes. Survivors of hereditary retinoblastoma had a greater than threefold excess of mortality from causes other than retinoblastoma, compared with the general population. This increased risk was primarily due to the 57 deaths from second malignancies (SMR = 12.8; 95% CI, 9.66–16.5). Among hereditary retinoblastoma patients, mortality from causes of death other than cancer was not significantly elevated compared to the Dutch population (SMR = 1.10; 95% CI, 0.60–1.84). Compared to the Dutch population, survivors of non-hereditary retinoblastoma experienced similar mortality from causes other than retinoblastoma (SMR = 1.01; 95% CI, 0.77–1.28). Among non-hereditary retinoblastoma patients no significantly elevated risks for any cause of death were found (Table 2).

In Table 3 the cancer site-specific mortality results of hereditary and non-hereditary retinoblastoma patients are presented. Compared with the Dutch population, hereditary retinoblastoma patients had higher mortality from cancers of the bone (SMR = 289) and soft tissue (SMR = 276). Elevated risks were also found for lung cancer (SMR = 6.85), bladder cancer (SMR = 37.2) and all other epithelial cancers combined (12 deaths, SMR = 8.91). For breast cancer and melanoma, risks were calculated in the group of 998 retinoblastoma patients at risk of death from 1901. Compared to the Dutch general population, hereditary retinoblastoma patients showed a higher mortality from melanoma (SMR = 31.3), but also from breast cancer (SMR = 5.23). Non-hereditary retinoblastoma patients had similar overall cancer mortality as the general population (SMR = 1.09); no significantly increased mortality for any site-specific cancer was found. Analysis of mortality by sex showed that mortality due to second malignancies did not differ between sexes for all retinoblastoma patients.

We found significantly elevated mortality rates from second malignancies among hereditary retinoblastoma patients during all intervals of follow-up (Table 4). During the first three decades after retinoblastoma diagnosis, the SMR for second malignancies increased from 25.4 to 61.1. After more than 30 years of follow-up, the SMR declined to 6.55 for patients surviving more than 50 years. This decline in the SMR may reflect an increasing baseline cancer mortality rate with age. The absolute excess risk increased significantly with longer time after diagnosis, up to 23.2 excess deaths per 1000 patients/year after 50 years of follow-up.

Table 5 lists out mortality from second malignancies among hereditary retinoblastoma patients by therapy. SMRs were statistically significantly elevated for hereditary retinoblastoma patients treated with both radiotherapy and chemotherapy (SMR = 60.9), radiotherapy alone (SMR = 18.1) and surgery alone (SMR = 7.95). The major causes of cancer-specific death for hereditary patients treated with radiotherapy were bone cancer and soft tissue sarcoma (70%). Among

Table 2 – Causes of death among all retinoblastoma patients, and among those who died after 1st January 1961, with SMRs.

Cause	ICD 10	Total (from 1901)	Hereditary[a] (from 1961)			Non-hereditary[a] (from 1961)		
		O (%)	O	SMR	95% CI	O	SMR	95% CI
Infectious diseases	A00–B99	3 (0.9)	0	0	0–11.4	0	0	0–5.06
Retinoblastoma	C69.2	156 (47.0)	20	3578	2186–5526	20	1210	739–1868
Second malignancies	C00–C97	84 (25.3)	57	12.8	9.66 to16.5	18	1.09	0.64–1.72
Benign tumours	D10–D36	1 (0.3)	1	39.0	0.99–217	0	0	0–66.2
Neoplasms of uncertain or unknown behaviour	D37–D48	2 (0.6)	1	9.90	0.25–55.2	1	3.04	0.08–16.9
Endocrine, nutritional and metabolic diseases	E00–E90	1 (0.3)	0	0	0–8.88	1	0.72	0.02–4.00
Mental disorders	F00–F99	1 (0.3)	1	8.13	0.21–45.3	0	0	0–5.20
Diseases of the nervous system and sense organs	G00–H95	4 (1.2)	0	0	0–6.35	2	1.44	0.17–5.20
Diseases of the circulatory system[b]	I00–I99	32 (9.6)	7	1.80	0.72–3.71	22	1.16	0.72–1.75
Cardiovascular disease	I21–I24; I30–I52	21 (6.3)	4	1.48	0.40–3.79	17	1.59	0.93–2.55
Cerebrovascular accident	I60–I69	5 (1.5)	1	1.36	0.03–7.58	2	0.53	0.06–1.90
Diseases of the respiratory system	J00–J99	3 (0.9)	1	1.12	0.03–6.21	2	0.48	0.06–1.72
Diseases of the digestive system	K00–K93	5 (1.5)	1	1.69	0.04–9.39	2	1.01	0.12–3.64
Diseases of the musculoskeletal system and connective tissue	M00-M99	1 (0.3)	0	0	0–49.2	1	3.75	0.09–20.9
Diseases of the genitourinary system	N00–N99	1 (0.3)	0	0	0–26.5	0	0	0–4.89
Congenital anomalies	Q00–Q99	4 (1.2)	1	0.43	0.01–2.42	3	0.97	0.20–2.83
Ill-defined conditions and unknown	R00–R99	2 (0.6)	0	0	0–3.31	0	0	0–1.31
External causes of injury and poisoning[c]	S00–T98; V01–Y98	16 (4.8)	3	1.29	0.27–3.76	5	1.03	0.33–2.40
No death certificate[d]		16 (4.8)	5	–	–	7	–	–
All causes other than retinoblastoma[e]		160 (48.2)	78	3.70	2.93–4.62	64	1.01	0.77–1.28
All causes other than cancer[f]		73 (22.0)	14	1.10	0.60–1.84	38	0.92	0.65–1.26

Abbreviations: ICD 10, International Classification of Diseases 10th revision; O, observed; SMR, standardised mortality ratio. Percentages may not add up to 100 due to rounding.

a For the hereditary group a total of 337 patients were included (person-years at risk = 8521). For the non-hereditary group a total of 512 patients were included (person-years at risk = 15,360).

b Includes among hereditary retinoblastoma survivors two deaths due to the diseases of arteries, arterioles and capillaries, and among non-hereditary retinoblastoma survivors one death due to chronic rheumatic heart disease, one due to the disease of pulmonary circulation and one due to the disease of arteries, arterioles and capillaries.

c Includes two deaths among hereditary retinoblastoma survivors (from 1961) due to suicide (SMR = 3.49; 95% CI, 0.42–12.6), and among non-hereditary retinoblastoma survivors (from 1961) three deaths due to suicide (SMR = 1.58; 95% CI, 0.19–5.72).

d SMRs could not be calculated because no reference rates were available.

e Includes all causes of death, excluding retinoblastoma, and those without a death certificate.

f Includes all causes of death, excluding death due to any type of cancer (malignant, benign, uncertain or unknown), and those without a death certificate.

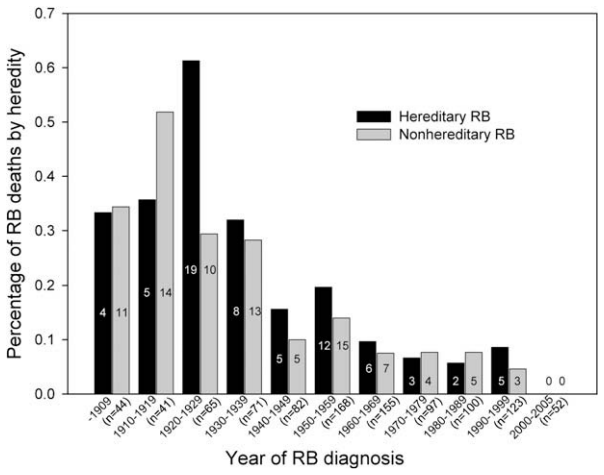

Fig. 1 – Percentage of retinoblastoma (RB) death by year of diagnosis and heredity; *n* = number of subjects diagnosed in each period; numbers in bars represent the observed number of retinoblastoma deaths among those who were diagnosed in that period.

hereditary patients treated with surgery alone, most cancer deaths (71%) were due to epithelial cancers. In Cox model analysis adjusted for age, the hazard ratio (HR) of second malignancy death associated with radiotherapy was non-significantly increased among hereditary retinoblastoma survivors (HR = 1.57; 95% CI, 0.83–2.95).

The cumulative mortality from second malignancy at 50 years after retinoblastoma diagnosis, adjusted for competing risks of death, was 17.3% (95% CI, 12.3–22.4%) for hereditary retinoblastoma survivors. For non-hereditary retinoblastoma patients, the cumulative mortality at 50 years after retinoblastoma diagnosis was 1.8% (95% CI, 0.47–3.29%). Among hereditary retinoblastoma patients, the cumulative mortality at 50 years after retinoblastoma diagnosis was 22.2% (95% CI, 13.9–30.5%) for those treated with radiotherapy and 12.2% (95% CI, 6.13–18.3%) for those treated otherwise.

4. Discussion

To our knowledge, this is the first study that evaluates mortality among retinoblastoma patients in a nationwide cohort with very long-term follow-up and near complete cause of death information. Statistically significantly elevated risks of death were only found for second malignancies among hereditary retinoblastoma survivors, with an almost 13-fold increase of second malignancy death compared with general population expectations. During follow-up, the AER increased and amounted to 23.2 deaths per 1000 patients/year after more than 50 years of follow-up. No significantly elevated mortality risks were found among the non-hereditary retinoblastoma survivors.

Consistent with findings in other studies,[7,14,15] neither hereditary nor non-hereditary retinoblastoma survivors experienced significantly elevated risks of mortality from non-cancer causes, such as infectious diseases, endocrine, nutritional and metabolic diseases, mental disorders, diseases of the nervous system and sense organs, diseases of the circulatory system, diseases of the respiratory system, diseases of the digestive system, diseases of the musculoskeletal system and connective tissue, diseases of the genitourinary system,

Table 3 – Risk of cancer mortality in Dutch retinoblastoma survivors by heredity.

Cancer site[b]	Hereditary retinoblastoma patients[a] (*n* = 337)				Non-hereditary retinoblastoma patients[a] (*n* = 512)			
	O	SMR	95% CI	AER[c]	O	SMR	95% CI	AER[c]
All sites (*malignant only*)	57	12.8	9.66–16.5	6.17	18	1.09	0.64–1.72	0.09
Bone	11	289	144–517	1.29	0	0	0–46.5	–0.00
Connective and Soft tissue	13	276	147–472	1.52	1	8.78	0.22–48.9	0.06
Skin melanoma[d]	3	31.3	6.46–91.5	0.26	0	0	0–14.6	–0.01
Bladder	3	37.2	7.67–109	0.34	2	4.54	0.55–16.4	0.10
Lung	7	6.85	2.75–14.1	0.70	7	1.54	0.62–3.18	0.16
Breast[d]	3	5.23	1.08–15.3	0.20	1	0.69	0.02–3.84	–0.02
All other epithelial cancers[e]	12	8.91	4.61–15.6	1.25	5	2.80	0.91–6.54	0.21

Abbreviations: ICD-O-3, International Classification of Diseases for Oncology third edition; O, observed number of cases; SMR, standardised mortality ratio; CI, confidence interval; AER, absolute excess risk (observed number of cancers minus expected number of cancers per person-years multiplied by 1000).

a Person-years at risk in the hereditary group; 8521. Person-years at risk in the non-hereditary group; 15,360.

b Cancer sites not listed for hereditary retinoblastoma patients include two cancers of the brain (no pinealoblastoma) (ICD-O-3 C71, SMR = 10.6; 95% CI, 1.28–38.3; AER = 0.21 per 1000 person-years), two non-Hodgkin lymphomas (ICD-O-3 C83; SMR = 14.2; 95% CI, 1.72–51.2; AER = 0.22 per 1000 person-years) and two cancers not otherwise specified (ICD-O-3 C80; SMR = 9.63; 95% CI, 1.16–34.8; AER = 0.21 per 1000 person-years). Cancer sites not listed for non-hereditary retinoblastoma patients include one Multiple Myeloma (ICD-O-3 C90; SIR = 4.14; 95% CI, 0.10–23.1; AER = 0.05 per 1000 person-years) and one cancer not otherwise specified (ICD-O-3 C80; SMR = 1.17; 95% CI, 0.03–6.52; AER=0.009 per 1000 person-years).

c When an AER of –0.00 is reported, it indicates that the AER is smaller than $-9.99 * 10^{-03}$ per 1000 person-years.

d For skin melanoma and breast cancer reference rates from 1901 onwards were used. For these analyses from 1901 the total number of persons and person-years at risk for each patient group was as follows: hereditary patients, *n* = 395, 10,982 person-years; non-hereditary patients, *n* = 603, 19,879 person-years.

e Includes for hereditary retinoblastoma patients cancer of the stomach, small intestine, colon, pancreas, corpus uteri, ovary and prostate. For non-hereditary retinoblastoma patients it includes cancer of the pharynx, pancreas, prostate and kidney.

Table 4 – Risk of cancer mortality among hereditary retinoblastoma patients, according to time since retinoblastoma diagnosis.

Cancer site[b]	Time since retinoblastoma diagnosis[a]																							
	0–9 (n = 337)				10–19 (n = 265)				20–29 (n = 218)				30–39 (n = 172)				40–49 (n = 118)				50+ (n = 73)			
	O	SMR	95% CI	AER[c]	O	SMR	95% CI	AER[c]	O	SMR	95% CI	AER[c]	O	SMR	95% CI	AER[c]	O	SMR	95% CI	AER[c]	O	SMR	95% CI	AER[c]
All sites	5	25.4	8.24–59.3	1.59	5	37.1	12.0–86.7	2.04	11	61.1	30.5–109	5.55	8	20.2	8.74–39.9	5.03	8	9.61	4.16–19.0	7.70	20	6.55	4.00–10.1	23.2
Bone	2	373	45.1–1346	0.66	3	154	31.8–445	1.25	4	394	107–1008	2.05	1	244	6.17–1358	0.66	1	285	7.21–1587	1.07	0	0	0–638	–0.00
Connective and soft tissue	1	87.1	2.20–485	0.32	2	372	45.0–1341	0.84	5	777	252–1812	2.56	1	153	3.87–851	0.66	2	276	33.4–997	2.14	2	141	17.0–508	2.72
Skin melanoma[d]	0	0	0–3726	–0.00	0	0	0–1773	–0.00	1	88.8	2.25–495	0.49	2	85.2	10.3–308	1.26	0	0	0–149	–0.03	0	0	0–10.1	–0.05
Bladder	0	0	0–7233	–0.00	0	0	0–92221	–0.00	0	0	0–7849	–0.00	1	361	9.12–2009	0.66	0	0	0–425	–0.00	2	28.4	3.44–103	2.64
Lung	0	0	0–8384	–0.00	0	0	0–3448	–0.00	0	0	0–807	–0.00	1	26.6	0.67–148	0.64	2	12.5	1.52–45.3	1.98	4	4.75	1.29–12.2	4.33
Breast[d]	0	0	0–9708	–0.00	0	0	0–9970	–0.00	0	0	0–335	–0.00	0	0	0–46.0	–0.09	1	5.77	0.15–32.2	0.87	2	6.16	0.75–22.3	2.26
All other epithelial cancers[e]	0	0	0–653	–0.00	0	0	0–478	–0.00	0	0	0–146	–0.02	2	23.3	2.83–84.3	1.27	2	8.76	1.06–31.6	1.90	8	7.58	3.27–14.9	10.4

Abbreviations: ICD-O-3, International Classification of Diseases for Oncology third edition; O, observed number of cases; SMR, standardised mortality ratio; CI, confidence interval; AER, absolute excess risk (observed number of cancers minus expected number of cancers per person-years multiplied by 1000).

a Person-years at risk in each period were as follows: 0–9 years, 3025 person-years; 10–19 years, 2385 person-years; 20–29 years, 1949 person-years; 30–39 years, 1512 person-years; 40–49 years, 932 person-years; 50+ years, 730 person-years.

b Cancer sites not listed includes in the 0–9 years interval two non-Hodgkin lymphomas (ICD-O-3 C83; SMR = 162; 95% CI, 19.6–585), in the 20–29 years interval one brain cancer (ICD-O-3 C71; SMR = 52.0; 95% CI, 1.32–290), in the 40–49 years interval one brain cancer (ICD-O-3 C71; SMR = 25.5; 95% CI, 0.65–142) and in the 50+ y interval two cancers not otherwise specified (ICD-O-3 C80; SMR = 12.9; 95% CI, 1.56–46.6).

c When an AER of –0.00 is reported, it indicates that the AER is smaller than $-9.99 * 10^{-03}$ per 1000 person-years.

d For skin melanoma and breast cancer reference rates from 1901 onwards were used. For these analyses from 1901 the total number of persons and person-years at risk in each period was as follows: 0–9 years, n = 395, 3252 person-years; 10–19 years, n = 272, 2455 person-years; 20–29 years, n = 225, 2019 person-years; 30–39 years, n = 179, 1566 person-years; 40–49 years, n = 121, 945 person-years; 50+ years, n = 74, 743 person-years.

e Includes for the 30–39 years interval cancer of the small intestine and colon, in the 40–49 years interval cancer of the small intestine and ovary, and in the 50+ years interval cancer of the stomach, colon, pancreas, corpus uteri, ovary and prostate.

Table 5 – Risk of cancer mortality in hereditary retinoblastoma patients by therapy for retinoblastoma.

Cancer site[b]	Treatment for retinoblastoma[a]											
	EBRT (n = 145)				EBRT and chemotherapy (n = 56)				Surgery (n = 112)			
	O	SMR	95% CI	AER[c]	O	SMR	95% CI	AER[c]	O	SMR	95% CI	AER[c]
All sites	15	18.1	10.1–29.9	3.85	12	60.9	31.5–106	8.34	27	7.95	5.24–11.6	7.53
Bone	4	266	72.2–680	1.08	4	659	179–1686	2.82	2	124	15.1–449	0.63
Connective and soft tissue	5	311	101–725	1.36	6	940	345–2064	4.23	2	85.2	10.3–308	0.63
Skin melanoma[d]	2	71.9	8.71–260	0.48	0	0	0–402	–0.00	1	17.3	0.44–96.6	0.19
Bladder	2	215	26.1–777	0.54	0	0	0–2120	–0.00	1	14.4	0.36–80.0	0.30
Lung	1	6.48	0.16–36.1	0.23	1	39.4	1.00–219	0.69	5	5.96	1.93–13.9	1.33
Breast[d]	0	0	0–33.7	–0.03	0	0	0–212	–0.01	3	6.91	1.42–20.2	0.51
All other epithelial cancers[e]	0	0	0–19.0	–0.05	0	0	0–101	–0.03	12	10.9	5.62–19.0	3.47

Abbreviations: ICD-O-3, International Classification of Diseases for Oncology third edition; EBRT, external beam radiation therapy; O, observed number of cases; SMR, standardised mortality ratio; CI, confidence interval; AER, absolute excess risk (observed numbers of cancers minus expected number of cancers per person-years multiplied by 1000).

a Not listed are chemotherapy with one non-Hodgkin lymphoma (ICD-O-3 C83; SMR = 3143; 95% CI, 79.5–17,504), 16 subjects and 125 person-years. Also not listed are those patients with an unknown treatment with one bone cancer (ICD-O-3 C40; SMR = 1606; 95% CI, 40.6–8946) and one cancer not otherwise specified (ICD-O-3 C80; SMR = 689; 95% CI, 17.4–3840), 8 subjects and 165 person-years. Person-years at risk in each treatment group were as follows: EBRT, 3679 person-years; EBRT and chemotherapy, 1416 person-years; Surgery, 3136 person-years.

b Cancer sites not listed includes one non-Hodgkin lymphoma in the EBRT group (ICD-O-3 C83; SMR = 29.6; 95% CI, 0.75–165), one brain cancer in the EBRT and chemotherapy group (ICD-O-3 C71; SMR = 51.7; 95% CI, 1.31–288), one brain cancer in the surgery group (ICD-O-3 C71; SMR = 9.36; 95% CI, 0.24–52.1) and one cancer not otherwise specified (ICD-O-3 C80; SMR = 6.11; 95% CI, 0.15–34.1).

c When an AER of –0.00 is reported, it indicates that the AER is smaller than $-9.99 * 10^{-03}$ per 1000 person-years.

d For skin melanoma and breast cancer reference rates from 1901 onwards were used. For these analyses from 1901 the total number of persons and person-years at risk for each treatment group was as follows: EBRT, n = 164, 4081 person-years; EBRT and chemotherapy, n = 58, 1468 person-years; Surgery, n = 140, 5049 person-years.

e Includes cancer of the stomach, small intestine, colon, pancreas, corpus uteri, ovary and prostate.

congenital anomalies, ill-defined conditions and unknown, and external causes of injury and poisoning. As expected, significantly elevated risks for mortality from second malignancies were only found among hereditary retinoblastoma survivors. SMRs for second malignancies of all causes differ substantially across studies, with SMRs of 5.41 (95% CI, 3.88–7.34),[7] 25.72 (95% CI, 17.38–38.07)[14] and 35 (95% CI, 30–41).[15] Our observed SMR of 12.8 differs substantially from the SMRs found in the above-mentioned studies. In the study by Acquaviva and colleagues,[14] there may be an overestimation of the SMR due to incompleteness of the follow-up. The study by Fletcher and colleagues[7] may have underestimated the risk, due to incompleteness of the British National Health Service Central Register (NHSCR) for deaths under the age of 25. Another possible explanation for the low SMR in the British cohort can be the treatment for retinoblastoma. Because the cohort consisted of retinoblastoma patients born between 1873 and 1950, only few patients had been treated with radiotherapy. Consequently, the low SMR for second malignancies may be explained by near absence of radiotherapy-induced tumours.[7] In contrast, the recent study by Yu and colleagues[15] reports a high SMR among hereditary retinoblastoma survivors (SMR = 35), which may be attributed to the high proportion of irradiated hereditary retinoblastoma survivors (87.5%) and, consequently, the high proportion (72.8%) of malignancies at heavily irradiated sites ($\geqslant$1 Gy).

According to our results, there are no differences in cancer mortality between females and males with hereditary retinoblastoma. Yu and coworkers[15] only found a strikingly elevated SMR among irradiated females, compared with males, for cancers of the brain and other parts of the nervous system. This is in contrast with their previous mortality report,[20] in which they found a higher overall mortality from second malignancies among females. The excess risk among females in the report by Yu and colleagues[15] may have been chance finding, however, since numbers were small.

In our study non-hereditary retinoblastoma survivors did not experience significantly elevated risks from any cause of death compared to the general population. However, several studies reported significantly elevated risks of mortality from second malignancies among non-hereditary retinoblastoma survivors.[14,15] In one of these studies,[14] this elevated risk was based on only four cancers that occurred among non-hereditary retinoblastoma with a median follow-up of 13 years. Our study had substantial longer follow-up and a larger number of expected cases, which results in more precise risk estimates for non-hereditary retinoblastoma survivors. In the other study an excess mortality from second malignancies among unilateral retinoblastoma survivors was observed.[15] In that study, the increased risk may be partly explained by radiation therapy and the possible misclassification of non-hereditary retinoblastoma survivors. According to our results, cancer mortality among non-hereditary retinoblastoma survivors is comparable with the general population (SMR = 1.09), suggesting that most, if not all, non-hereditary patients did not have a *RB1*-mutation and were not exposed to radiotherapy. Although family history of all non-hereditary retinoblastoma survivors was available, genetic information on the *RB1*-mutation was not available for most patients.

The treatments administered to retinoblastoma patients have changed substantially over the past century,[10,21–23] resulting in higher survival rates of the disease,[24] but differed

between countries.[25–27] The majority of retinoblastoma patients in our cohort were treated with surgery alone, in particular the non-hereditary patients. Most hereditary retinoblastoma patients were treated with radiotherapy alone, or with a combination of radiation and chemotherapy. Furthermore, some patients were successfully treated with brachytherapy, chemotherapy, coagulation or cryotherapy.[13]

For hereditary retinoblastoma survivors treated with radiotherapy, with or without chemotherapy, strongly elevated SMRs were observed. More than 70% of all deaths among irradiated survivors were due to bone cancer or soft tissue sarcoma. By contrast, deaths among patients treated otherwise (i.e. by surgery alone), were mostly due to epithelial cancers. As is known from long-term follow-up incidence studies,[6,9,13] retinoblastoma patients treated with radiotherapy have increased risks of developing second malignancies compared to hereditary retinoblastoma patients treated otherwise. Radiation-related second malignancies among hereditary retinoblastoma survivors, such as bone cancer and soft tissue sarcomas occur at earlier ages than most other cancer types.[6,8,10,11,20] Most radiation-induced bone cancers and soft tissue sarcomas originate within the field of irradiation, and most of these malignancies are difficult to treat,[28] which in most cases leads to death. In our cohort most deaths from bone cancer or soft tissue sarcoma in hereditary retinoblastoma survivors occurred within 30 years after retinoblastoma diagnosis, which is similar to results obtained from another study on mortality by time interval.[15] According to another report,[7] hereditary retinoblastoma patients mostly died due to epithelial cancers observed at non-irradiated sites. In our study we observed both effects: hereditary retinoblastoma survivors treated with radiotherapy who died relatively young from bone cancers and soft tissue sarcomas, and hereditary retinoblastoma survivors not treated with radiotherapy who died at older ages because of epithelial cancers. This explains the only moderately and non-significantly elevated mortality among patients treated with radiotherapy or otherwise (HR = 1.57; 95% CI, 0.83–2.95).

In the Netherlands very old population reference rates for breast cancer and skin melanoma mortality were available. These old rates gave us the opportunity to calculate SMRs among all retinoblastoma survivors who were at risk after 1901. For both melanoma and breast cancer only three deaths occurred, but the SMRs were significantly elevated compared with the general population (SMR = 31.3 and 5.23, respectively). Of all long-term follow-up studies on the incidence of second malignancies among hereditary retinoblastoma survivors, only two studies found an excess risk for breast cancer among females who had been treated with radiotherapy.[9,13] In the present study, a statistically significant excess of breast cancer mortality was found among hereditary retinoblastoma females. These breast cancers occurred in females who had not been irradiated for their retinoblastoma, and the breast cancer deaths occurred after more than 50 years of follow-up. In combination with our significantly raised breast cancer incidence among irradiated females in our Dutch retinoblastoma cohort after follow-up of more than 40 years,[13] we conclude that the risk of breast cancer in older females with hereditary retinoblastoma is elevated compared to the general population, irrespective of treatment for retinoblastoma.

Certain features of our study should be considered when interpreting the results. Despite our very complete follow-up of retinoblastoma patients diagnosed from 1862 to 2005 in the Netherlands, cause-specific population reference rates for almost all causes of death were not available before 1961. Furthermore, subgroup analyses were based on relatively small numbers of death, even though this is one of the largest long-term follow-up studies of retinoblastoma patients. Another limitation of our study is the potential misclassification of non-hereditary patients due to an incomplete chromosomal/DNA analysis.

An elevated incidence of a malignancy does not always result in an equally elevated risk of death. Previously, we described in hereditary retinoblastoma survivors diagnosed between 1945 and 2005 a standardised incidence ratio (SIR) for second malignancies of 20.4 (95% CI, 15.6–26.1) and a cumulative incidence of 28% at 40 years after retinoblastoma diagnosis.[13] As a result of early detection and good treatment options for cancers occurring outside the head,[29] a SMR of 12.8, and a cumulative mortality of 17.3% after 50 years of retinoblastoma diagnosis were observed in this study. Nevertheless, the emerging excess risk of mortality in retinoblastoma survivors is a cause of concern, and indicates that lifelong follow-up is needed to evaluate the full spectrum of subsequent mortality risk in hereditary retinoblastoma survivors. At the same time, patients and their physicians must be alerted to the increased second malignancy risk among hereditary retinoblastoma survivors.

Conflict of interest statement

None declared.

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